REMARKS/ARGUMENTS

Objections to the Specification

The Examiner has maintained the objections to the specification. Applicants submit herewith amendments to each of the sections noted by the Examiner in the initial objection. Applicants respectfully request entry of the amendments and reconsideration of the objections.

Status of the Claims

Claims 7, 8, 11, 12, 22, and 23 are pending. Claim 7 is amended to correct a grammatical error and as suggested by the Examiner. Claim 12 includes minor amendments that are not intended to change the subject matter of the claim. No new matter is added.

Applicants appreciate the explicit withdrawal of the rejections for alleged lack of enablement and anticipation. The remaining issues are addressed in the order presented in the August 25, 2009 Office Action.

Objection to the Claims

The Examiner has objected to claim 7 as allegedly lacking precedent basis for the term "said treatment." Claim 7 is amended as suggested, to delete the word "said." Applicants respectfully request withdrawal of the objection.

Rejection Under 35 USC § 103

The Examiner has rejected claims 7, 8, 11, 12, 22, and 23 as allegedly obvious over Shinomiya *et al.* (1979) *J. Virol.* 32:958-67 in view of Haas *et al.* (1974) *J. Infectious Dis.* 129:470-72. According to the Examiner, Shinomiya teaches that an isolated phage tail of PS17 has bacteriocidal activity against *P. aeruginosa* PML14, and that bacteriophage tails might act similar to pyocins. The Examiner alleges that Haas teaches that pyocins are therapeutically effective against *P. aeruginosa* infections in mice, and that *in vitro* killing activity correlates with *in vivo* protective effect. According to the Examiner, one of skill would be motivated to combine

the teachings of Haas with the phage tail as taught by Shinomiya to arrive at the present invention.

Legal standard

A *prima facie* case of obviousness requires the examiner to establish that one of skill in the art would have a reasonable expectation of success in making the claimed invention (*see* MPEP § 2143.02). The Supreme Court, in *KSR*, reaffirmed the importance of predictability in determining obviousness (*see* MPEP 2141, where the word "predictable" features prominently among potential rationales for a *prima facie* case).

Predictability is based on the person of ordinary skill at the time of the invention. Indeed, the MPEP 2142 explains that the examiner must step backward in time and into the shoes worn by the hypothetical person of ordinary skill in the art when the invention was unknown.

The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness, *i.e.*, establishing a reasonable expectation of success. If the examiner produces a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the applicant. The applicant may submit additional evidence of nonobviousness, such as unexpected or surprisingly effective results or long-felt but unmet need (MPEP 2142). MPEP 2141.02 emphasizes that prior art must be considered in its entirety, including disclosures that teach away from the claims.

One of skill would not have a reasonable expectation that a composition comprising phage tails would effectively reduce bacterial infection in vivo

The present claims are directed to methods of reducing a bacterial population in a subject using phage tail compositions. The Examiner has failed to establish that one of skill in the art at the time of the invention would reasonably expect success using phage tails to treat an existing bacterial infection, given the teaching of Shinomiya and Haas.

Haas teaches that pyocins have a prophylactic, but ***not*** a therapeutic, effect on bacterial infections in mice. Table 1 shows that pyocin injection prior to bacterial challenge reduced mortality significantly, while injection after bacterial challenge did not reduce mortality. Haas does cite a reference that apparently describes therapeutic use of pyocins, but itself discloses that pyocin treatment of an existing bacterial infection results in 100% mortality, indicating no therapeutic effect. As stated on page 470 of Hass, under Results:

> [I]njection of pyocin after challenge had no effect on mortality.

Thus, Haas at most teaches that it was unpredictable whether pyocins were effective for treating a bacterial infection *in vivo*.

Shinomiya compares phage tails to pyocins *in vitro*, and concludes that phage tails are much less efficient than pyocins for this purpose. At the bottom of the first column, page 966, Shinomiya found that 200 PEUs (phage equivalent units) of phage tails were required to kill a single bacterium, while only a few pyocins per bacterium are required. To quote the reference:

> The reason why the efficiency of killing by the isolated tail is so low is not clear.

In sum, the art teaches that **pyocins are not effective for treating an existing bacterial infection** *in vivo*, and that **phage tails are much less efficient antibacterial agents than pyocins** for killing bacteria *in vitro*. One of skill would have no motivation to use an antibacterial agent that has been shown to be inefficient *in vitro* and use it *in vivo*. This is especially true when the supposedly more efficient agent (pyocin) is shown to be ineffective for treatment of an existing bacterial infection.

While Applicants respectfully dispute the existence of a *prima facie* case of obviousness, we turn now to unexpected properties of the present invention.

Phage tails provide unexpected results

The compositions recited in the claims provide the unexpected advantage of having a broad host range, and thus a wider range of therapeutic targets.

Shinomiya teaches that phage tails have the same specificity as the intact phage. Indeed, Table 2 shows a very specific pattern of sensitivity of each strain of PS17 bacteria to various pyocins and phage compositions. To quote again from the reference, page 964:

> **As expected**, the pattern of [bacterial] strains sensitive to the tail was the same as that of PS17 phage and different from that of any R-type pyocin. (emphasis added)

Shinomiya expected a certain result and found it. In contrast, the present specification shows the **unexpected** result that tails have a different host range from intact phage.

This phenomenon is described in Example 3D of the specification (starting on page 49). The section explains that, while intact P954 bacteriophage can infect, *i.e.*, bind to, a spectrum of *S. aureus* isolates, it is unable to propagate, and thus lyse, the entire range of these isolates. This is due to a prophage in the *S. aureus* strains that prevents superinfection by more than one phage ("immunity to superinfection").

Example 3D goes on to describe the results of a killing assay on seven different *S. aureus* isolates, comparing intact P954 phage to P954 phage tails. While the susceptibility of each strain was about 30% for the intact phage, it was over 90% for the phage tails.

Example 4E (starting on page 52) shows the results of a similar experiment with 32 strains of *S. aureus*. Again, the phage tails demonstrated killing activity in nearly all strains tested, while the intact phage was only able to lyse 4 of the 32 strains.

These examples demonstrate a narrow host range for intact phage. The present phage tail compositions, however, can effectively reduce infection of a much broader range of pathogens than expected.

Conclusion

The cited references do not provide a reasonable expectation of success in treating a bacterial infection *in vivo* using a phage tail composition. Shinomiya teaches that tails are not efficient bactericidal agents, even *in vitro*. Haas teaches that pyocins are not effective for treatment of an existing bacterial infection *in vivo*. In addition, the present phage tail

compositions provide the unexpected advantage of having a broad host range. In view of the foregoing comments, Applicants respectfully request withdrawal of the rejection under 35 USC § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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